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Review

Orthostatic hypotension and cognition in older adults: A systematic review and meta-analysis

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ABSTRACT

Background: Orthostatic hypotension (OH) is common in older adults with reported prevalence rates of 5–40%. A direct link between OH and cognitive performance has been proposed due to impaired vascular autoregulation.

Aim: To systematically assess the literature of the association between OH and cognitive performance in older adults.

Methods: Literature search of MEDLINE, Embase, Cochrane Central Register of Controlled Trials and PsycINFO from inception to May 2017. Studies were included if OH and cognition were assessed in subjects of mean or median age ≥65 years. Risk of bias was assessed with the Newcastle Ottawa Scale.

Results: Of 3266 studies screened, 32 studies (22 cross-sectional; 10 longitudinal) reporting data of 28,980 individuals were included. OH prevalence ranged from 3.3% to 58%. Of the 32 studies, 18 reported an association between OH and worse cognitive performance and 14 reported no association. Mini Mental State Examination (MMSE) was the most commonly used cognitive assessment tool. Studies using more than one cognitive assessment tool were more likely to find an association between OH and worse cognition. OH was significantly associated with a lower MMSE mean score (mean difference − 0.51 (95% CI: −0.85, −0.17, $p = 0.003$)) and an increased risk of cognitive impairment (OR 1.19 (95% CI, 1.00–1.42, $p = 0.048$)).

Conclusions: OH is common in older populations and is associated with worse cognition expressed as lower MMSE scores. Use of MMSE alone as a cognitive assessment tool may underestimate the association. It is yet unclear whether the association between OH and worse cognitive performance is causative.

1. Introduction

Orthostatic hypotension (OH) is common in older adults with prevalence rates ranging from 6% in healthy older adults (Joseph et al., 2017a), 15% in geriatric outpatients and up to 41% in patients with dementia (Sonnesyn et al., 2009; Low, 2008). Current management of OH in clinical settings is largely dependent on the presence of orthostatic symptoms such as dizziness, fatigue, headache and blurred vision (Joseph et al., 2017b), however a third of older adults with OH are asymptomatic (Arbogast et al., 2009). The diagnosis of OH is important due to its association with poor clinical outcomes in older adults, including all cause and cardiovascular mortality (Ricci et al., 2015; Luukinen et al., 1999; Liguori et al., 2018), impaired standing balance (de Bruine et al., 2018) (Mol et al., 2018), increased falls (Gupta and Lipsitz, 2007; Novak and Hajjar, 2010; Peralta et al., 2007; Mol et al., 2018a) and impaired of Activity of Daily Living performance (Mol et al., 2018).

Despite the high prevalence of OH in older adults with dementia (Passant et al., 1996), there is conflicting evidence on the relationship between OH and cognitive performance. A possible association between OH and worse cognition is suggested by evidence of dysregulation of cerebral blood flow in OH (Biogeau et al., 2017) and MRI changes of silent cerebral infarcts and deep white matter lesions associated with OH (Kario et al., 2002).

The aim of this study was to systematically review the current literature to determine the association between OH and cognition in older adults in comparison to those without OH. Additionally, a meta-analysis was performed to provide a pooled, combined estimate of the

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association between OH and cognitive performance.

2. Methods

The protocol of the systematic review was developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al., 2009) and registered with the PROSPERO International prospective register of systematic reviews (CRD42017078403). MEDLINE (from 1946), EMBASE (from 1974), Cochrane Central Register of Controlled Trials (from inception) and PsycINFO (from 1806) databases were systematically searched for studies published until May 2017. The search strategy included the following key words: “orthostatic hypotension”, “orthostasis”, “orthostatic blood pressure”, “cognition”, “old”, “cognitive impairment” and synonyms. The complete search strategy for each database is included in Appendix A.

2.1. Study selection

Studies were managed with EndNote (Version: X8.2 Clarivate Analytics, Philadelphia, USA). Inclusion criteria were: article published in English; mean or median age ≥ 65 years; participants assessed for OH by consensus definition (a decrease of at least 20 mmHg systolic blood pressure (BP) and/or 10 mmHg diastolic BP within the first 3 min of standing) (Freeman et al., 2011); and, assessment of cognition was reported for cohorts with and without OH. Studies without primary data, such as conference abstracts and reviews, were excluded. For studies that reported mean age by cohort (for example, cohorts with and without OH), the study was included if the mean or median age of at least one cohort was ≥65 years.

2.2. Data extraction

Titles and abstracts were independently reviewed by two reviewers (VTVN, RI). Disagreements were resolved by discussion with a third reviewer (ABM, WKL, EMR). Full texts of included articles were independently assessed and data extraction performed by two reviewers (VTVN, RI).

2.3. Study quality

The quality and risk of bias of individual studies was assessed by two independent reviewers (VTVN, RI) using the Newcastle-Ottawa Scale (NOS) (Lo et al., 2014). The NOS provides an assessment of the methodological quality of case control and cohort studies with a maximum score of 9 points (Lo et al., 2014). All included studies were assessed using three criteria: 1) selection and representativeness of the subjects with and without OH, ascertainment of exposure, diagnosis of OH; 2) comparability of study groups: adjustment for potential confounders; and 3) outcome: assessment of cognition, adequacy of duration and completeness of follow-up. Studies with a NOS score between 0 and 3 points was defined as low quality, 4 to 6 points as moderate quality and 7 to 9 points as high quality (Hartog et al., 2017).

2.4. Meta-analysis

Meta-analyses were performed using Comprehensive Meta-analysis (version 2.0; Biostat Inc., Engle-wood, NJ), with a random effects model (Borenstein et al., 2010). The means and standard deviations (SD) were used for continuous cognitive assessment scale outcomes For the dichotomous outcome of diagnosis of cognitive impairment, the odds ratio (OR) for reported prevalence in the groups with and without OH was used. Subgroup analyses were stratified by study population. Heterogeneity was expressed using the I^2 statistic (low < 25%; moderate < 50%; high > 50%). *P* values below 0.05 were considered significant. An estimate of publication bias was calculated using Egger's test for meta-analyses of ten studies or more (Egger et al., 1997).

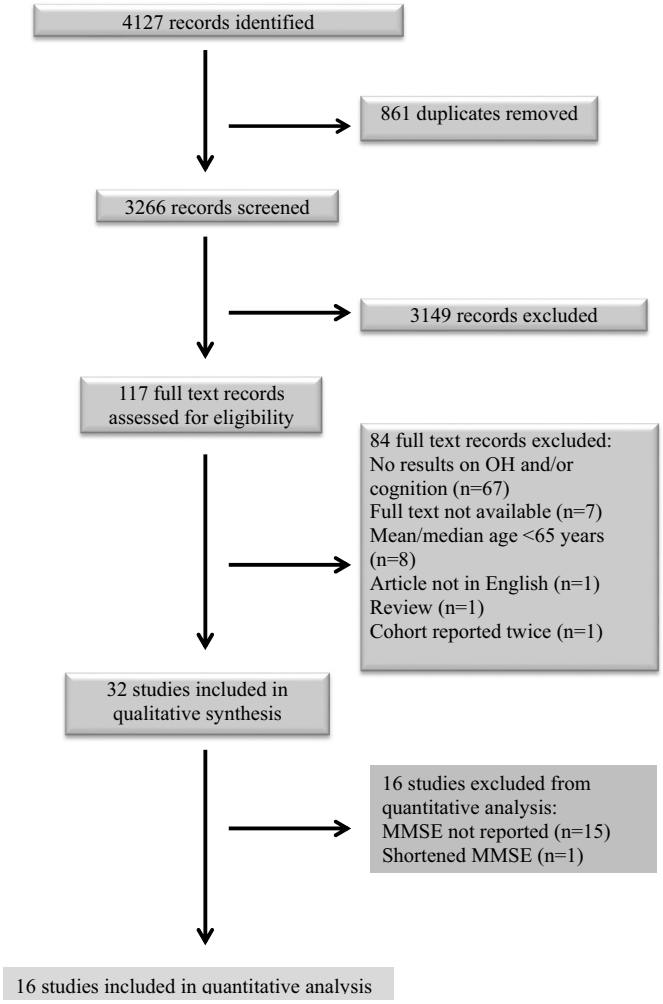

Fig. 1. Selection process shown through the PRISMA flow chart.

3. Results

Of 3266 studies eligible for title and abstract screening, 117 were eligible for full text screening and 32 studies were included in the systematic review. Fig. 1 shows the selection process of included studies.

3.1. Systematic review

Table 1 shows the descriptive characteristics of the included studies. The studies included a total of 28,980 individuals. Most studies (26 out of 32) were conducted in community-dwelling older adults, three studies included hospitalised older adults and three studies were of institutionalised older adults. Seven studies focused on OH and cognition in patients with Parkinson's Disease (PD). Most studies (27 out of 32) measured BP intermittently rather than continuously using beat to beat measurements. A majority (25 out of 32) of studies tested for OH using Active Stand Test (AST): one study did not report the method of testing (Otsuka et al., 2014) and one study performed both AST and Head Up Tilt (HUT) (Aydin et al., 2017). Table 2 shows the details of reported neuropsychological testing for each study. Mini Mental State Examination (MMSE) (Folstein et al., 1975) was the most frequently used cognitive assessment scale in 21 studies. Two or more cognitive assessment scales were reported in 16 studies: although the additional assessment scales varied, these studies were more likely to report an

Table 1
Study characteristics.

First author, year	Population	Study design	N	Age, years mean (SD)	Females, N (%)	Cognitive tests	OH and cognition association	OH prevalence (%)
(Agnoletti 2015a)	Institutionalised ≥80 years	P, C	972	88 (5)	748 (77)	MMSE	No	16.2
(Allcock 2006)	Parkinson's Disease	P, C	175	70.8 (8)	63 (36)	MMSE CDR battery	Digit vigilance/visual memory: Yes MMSE/dementia: No	49.7
(Aydin 2017)	Hospitalised ≥65 years	P, C	290	HUT: OH (+): 78.7 (8.1) OH (−): 73.9 (8.6) AST: OH (+): 75.7 (8.3) OH (−): 74.2 (9.0)	HUT: 173 (59.7) AST: 172 (59.3)	MMSE COST	OH diagnosed using HUT: Yes OH diagnosed using AST: No	HUT 19 AST 37
(Bengtsson-Lindberg 2015)	Memory clinic and community dwelling controls	P, C	204	76 (6)	N/A	MMSE	Yes	Overall 43 Dementia 53 Controls 13
(Biogeau 2017)	Hospitalised > 80 years	P, C	39	88.3 (0.9)	14 (35.9)	MMSE	No	56.4
(Bouhanick 2014)	Type II diabetes ≥70 years	P, C	987	OH (+): 77 (5) OH (−): 77 (5)	OH (+): 162 (54.0) OH (−): 349 (51.0)	MMSE	No	26.8
(Centi 2017)	PD outpatients with and without OH; normal controls	P, C	37	PD: 65.6 (9.5) PD OH: 64.3 (6.5) Controls: 62.9 (7.6)	PD: 8 (42.1) PD OH: 7 (38.9) Controls: 9 (50)	MMSE, WTAR, Stroop test, Digit Span Test, Arithmetic test, Verbal fluency, Symbol search test, CERAD verbal learning test	Yes, especially when tested upright	N/A
(Coutaz 2011)	Hospitalised older adults	P, C	340	OH (+): 81.3 (7.7) OH (−): 80.3 (8.59)	OH (+): 92 (63.9) OH (−): 141 (71.9)	MMSE	Yes	42.3
(Curreri 2016)	Community dwelling older adults, cognitively normal at baseline	P, L	1408	71.4 (5.2)	836 (59.4)	MMSE	No	18.3
(Enrique Asensio 2011)	Institutionalised 65 years and older	P, L	132	OH (+): 83.3 (9.4) OH (−): 82.2 (9.5)	OH (+): 30 (76.9) OH (−): 68 (72.3)	MMSE	No	29.3
(Elmstahl 2014)	Community dwelling	P, L	2931	68 (8.5)	1641 (56.0)	MCI and Dementia diagnosis	Yes	Overall 19 Controls 17 MCI 24 Dementia 34
(Feeney 2016)	Community dwelling 50 years and over	P, L	3416	No impaired OBP 60.9 (7.9) Impaired OBP 65.4 (9.1)	No impaired OBP: 1557 (52.4) Impaired OBP: 258 (57.8)	MMSE Verbal fluency 10-word recall task	No	13
(Frewen 2014)	Community dwelling 50 years and over	P, C	5936	OH (+) 67.2 (9.6) OH (−): 61.9 (9.3)	OH (+): 214 (59.6) OH (−): 2977 (53.8)	MMSE MOCA Verbal fluency Visual reasoning tasks Color Trail CRT Word recall test, Picture memory test SART	In 65 years and older group: Yes	9.3

(*continued on next page*)

Table 1 (*continued*)

First author, year	Population	Study design	N	Age, years mean (SD)	Females, N (%)	Cognitive tests	OH and cognition association	OH prevalence (%)
(Hayakawa 2015)	Memory clinic with diagnosis of MCI, community dwelling controls	P, L	216	MCI: 74 (6.8) Controls: 69 (7.1)	108 (50.0)	RBANS CAMCOG MMSE	Yes	MCI 12 Controls 1
(Huang 2017)	Geriatric unit outpatients and controls > 60 years	P, L	132	OH (+) 69.90 (6.03) OH (−) 68.92 (7.34)	OH (+): 16 (36.4) OH (−): 38 (43.2)	MMSE	Yes	N/A
(Idiaquez 2007)	PD patients and controls	P, C	70	69 (8.2)	26 (22.9)	MMSE FAB	No	All 8.6 PD 12.5 Controls 3.3
(Kim 2012)	Early PD outpatients	P, C	87	67.5 (9.2)	52 (59.8)	MMSE CDR Seoul Neuropsychological Screening Battery	Verbal immediate and delayed memory: Yes Higher prevalence of dementia and MCI in OH group	36.8
(Matsubayashi 1997)	Community dwelling 75 years and older	P, C	334	80 (5)	182 (54.5)	MMSE HDSR VCPS	HDSR and VCPS: Yes MMSE: No	6
(Mehrabian 2010)	Memory clinic	P, C	495	OH (+): 77 (6) OH (−): 76 (8)	OH (+): 45 (65.0) OH (−): 306 (72.0)	CEP	Yes	14
(O'Hare 2017b)	Community dwelling	P, L	240	72.30 (2.6)	142 (59.2)	Diagnosis of MCI and dementia based on neurology, neuropsychology and MRI	Yes: lower ASOBPR in groups diagnosed with MCI and dementia	10.4
(Otsuka 2014)	Community dwelling 75 years and older	P, C	691	81.0 (4.6)	454 (65.7)	MMSE	Yes	10.6
Peralta 2007	Parkinson's disease (PD) patients with and without dementia	P, C	18	PD 74.1 (4.8) PDD 77.3 (7.5)	N/A	During tilt testing: attention, word fluency	Attention: Yes Higher prevalence of dementia in OH group	38.9
Pilleri 2013	PD patients (hospitalised)	P, C	48	OH (+): 64.96 (9.7) OH (−): 65.6 (8.7)	22 (45.8)	MMSE FAB Neuropsychological battery (Digit Span, Corsi Test, Attentional Matrix, Trail Making Test, Rey Auditory Verbal Learning Test, Rey-Osterrieth Complex Figure Test)	Visuospatial working memory: Yes Attention: Yes Verbal memory: Yes MMSE: No	47.9
Punchick 2016	Geriatric outpatients	R, C	534	83.7 (6.1)	309 (57.9)	MMSE MoCA	No	32.1
Schoon 2013	Falls and syncope clinic	R, C	178	OH (+) 79.8 (6.7) OH (−) 80.4 (6.9)	OH (+): 69 (66.0) OH (−): 45 (61.0)	MMSE CAMCOG	No	58
(Soennesyn 2014)	Patients with first time diagnosis of mild dementia (MMSE > 19)	P, L	133	77.2	79 (59)	MMSE CDR-SB	No	Baseline 44; Follow up period 30–45
(Sonnesyn 2009)	Patients with mild dementia (MMSE > 19) and healthy controls	P, C	262	DLB: 78.1 (8.2) PDD 73.4 (8.8) AD 75.6 (7.7) VaD 74.7 (7.6)	168 (56)	MMSE (not reported by OH group) Dementia diagnosis IQCODE Hachinski ischemia scale	Yes: higher prevalence of OH in participants with dementia	Dementia 41 control 14
(Soysal 2014)	Geriatric outpatients 65 years and older	R, C	546	OH (+): 73.4 (9.2) OH (−) 73.3 (8.7)	OH (+): 97 (64.7) OH (−): 234 (59.1)	MMSE	No	27.5
(Umehara 2016)	PD outpatients	P, C	72	PD with OH: 73 (6) PD without OH: 72 (7)	PD OH: 22 (55.0) PD without OH: 22 (68.8)	MMSE FAB	No	55.5

(*continued on next page*)

Table 1 (*continued*)

First author, year	Population	Study design	N	Age, years mean (SD)	Females, N (%)	Cognitive tests	OH and cognition association	OH prevalence (%)
(Viramo 1999)	Institutionalised and home-dwelling older adults	P, L	907	OH (+): 76 (4.93) OH (−): 76.0 (5.10)	N/A	Shortened MMSE (total score 25)	No	31
(Wolters 2016b)	Community dwelling ≥ 55 years	P, L	6204	68.5 (8.6)	3704 (59.7)	MMSE GMS CAMDEX	Yes: OH associated with higher incidence dementia	18.6
(Yap 2008)	Community dwelling aged ≥ 55 years with no history of stroke or cardiovascular disease	P, L	2294	OH (+): 66.6 (8.5) OH (−): 65.3 (7.1)	OH (+): 259 (68.0) OH (−): 1249 (65.3)	MMSE	No	16.6

All variables are presented as mean (SD) unless indicated otherwise. P: prospective. R: retrospective. L: longitudinal. C: cross-sectional. OH: Orthostatic hypotension. MMSE: Mini Mental State Examination. PD: Parkinson's Disease. SRT: Simple reaction time. CRT: Choice reaction time. HUT: Head Up Tilt. AST: Active Standing Test. COST: Cognitive State Test (Babacan-Yildiz et al., 2013). WTAR: Wechsler Test of Adult Reading. MoCA: Montreal Cognitive Assessment. SART: Sustained Attention to Response Task. HDSR: Hasegawa Dementia Scale Revised. VCPS: Visuospatial Cognitive Performance Score. CEP: Cognitive Efficiency Profile. FAB: Frontal Assessment Battery. TMT: Trail Making Test. ROCF: Rey-Osterrieth Complex Figure. CAMCOG: Cognitive and self-contained part of the Cambridge Examination for Mental Disorders of the Elderly. CDR-SB: Clinical Dementia Rating Sum of Boxes. sMMSE: shortened Mini Mental State Examination. OR: Odds Ratio. GMS: Geriatric Mental State Schedule. MCI: Mild Cognitive Impairment. ASOBPR: average systolic orthostatic blood pressure response. WMH: white matter hyperintensities. MRI: Magnetic Resonance Imaging. CDR: Cognitive Drug Research computerised assessment system. RBANS: Repeatable Battery for Assessment of Neurological Status.

association between OH and worse cognition.

OH prevalence ranged from 3.3% to 58%: the highest prevalence rates were reported in falls and syncope clinic outpatients (Schoon et al., 2013), geriatric unit inpatients (Biogeau et al., 2017), PD (Allcock et al., 2006; Pilleri et al., 2013; Umehara et al., 2016) and dementia (Bengtsson-Lindberg et al., 2015); the lowest prevalence rates were reported in healthy older controls (Idiaquez et al., 2007; Hayakawa et al., 2015).

Of the 32 included studies, 18 reported a positive association between OH and worse cognition, based on either cognitive test score (Otsuka et al., 2014; Aydin et al., 2017; Allcock et al., 2006; Pilleri et al., 2013; Bengtsson-Lindberg et al., 2015; Frewen et al., 2014; Huang et al., 2017; Centi et al., 2017; Coutaz et al., 2012; Matsubayashi et al., 1997; Mehrabian et al., 2010; Peralta et al., 2007) or diagnosis of dementia (Hayakawa et al., 2015; Elmstahl and Widerstrom, 2014; Kim et al., 2012; O'Hare et al., 2017a; Sonnesyn et al., 2009; Wolters et al., 2016a) and 14 studies reported no association (Biogeau et al., 2017; Schoon et al., 2013; Umehara et al., 2016; Idiaquez et al., 2007; Agnoletti et al., 2015a; Bouhanick et al., 2014; Curreri et al., 2016; Punchick et al., 2016; Soennesyn et al., 2014; Soysal et al., 2014; Viramo et al., 1999; Yap et al., 2014; Asensio Lafuente et al., 2011; Feeney et al., 2016).

3.1.1. Longitudinal studies: does OH predict later cognitive impairment?

Of ten longitudinal studies, two studies reported multiple assessments for OH. O'Hare et al. (O'Hare et al., 2017b) tested community dwelling older adults for OH over 6 years and assessed cognitive status 14 years later with neuropsychological assessment and brain imaging. Average Systolic Orthostatic Blood Pressure Response (ASOBPR), the percentage change in systolic BP from sit to stand at 1 min post stand, was found to be lower for those with dementia compared to those with normal cognitive status. The odds of dementia diagnosis reduced by 9% with each percentage point rise in ASOBPR. Soennesyn et al. (Soennesyn et al., 2014) followed older individuals with mild-moderate dementia over 4 years, assessing cognitive decline using MMSE score and Clinical Dementia Rating sum of boxes (Hughes et al., 1982), and found no association between presence of OH and cognitive decline.

Eight longitudinal studies reported only a baseline measure of OH, with follow up of cognitive performance. The four studies that reported a positive association between OH and worse cognition had long follow up (3 to 25 years) and used detailed cognitive assessment scales (Hayakawa et al., 2015; Huang et al., 2017; Elmstahl and Widerstrom, 2014; Wolters et al., 2016a), whilst the 4 longitudinal studies that did not find a significant association between OH and cognitive impairment (Curreri et al., 2016; Viramo et al., 1999; Yap et al., 2014; Feeney et al., 2016) had shorter follow up (1–4 years) and used MMSE as the predominant cognitive assessment scale.

3.1.2. Cross-sectional studies: Is there an association between OH and cognitive impairment?

Seven cross-sectional studies examined the association between OH and cognitive impairment in patients with PD: five of these studies reported an association between OH and worse cognitive performance in areas of attention or memory on neuropsychological assessment, but none of the studies reported an association between OH and worse MMSE or Frontal Assessment Battery score (Allcock et al., 2006; Pilleri et al., 2013; Umehara et al., 2016; Idiaquez et al., 2007; Centi et al., 2017; Peralta et al., 2007; Kim et al., 2012; Dubois et al., 2000).

Of the fifteen remaining cross-sectional studies, eight reported an association between OH and worse cognitive performance. Studies reporting a positive association between OH and worse cognition were more likely to use additional cognitive assessment scales to the MMSE and to be prospective (Otsuka et al., 2014; Aydin et al., 2017; Bengtsson-Lindberg et al., 2015; Coutaz et al., 2012; Matsubayashi et al., 1997; Mehrabian et al., 2010; Sonnesyn et al., 2009; Frewen et al., 2014), whilst studies reporting no association were more likely to

Table 2
Summary of cognitive assessment tools and results stratified for presence of OH (n = 22).

First author, year	Cognitive test(s)	OH-positive	OH-negative
Agnoletti 2015	MMSE, score	23.2 ± 4.9	23.4 ± 5.1
Allcock 2006	MMSE, score, median [IQR]	25.0 [4.0]	26.0 [5.0]
	SRT, ms	389 [141]	394 [167]
	CRT, ms	554 [170]	561 (134)
	Digit vigilance accuracy, % median [IQR]	79 [31]	93 [16]
	Numeric working memory	0.80 ± 0.33	0.88 ± 0.29
	Verbal memory, median [IQR]	0.73 [0.20]	0.69 [0.28]
	Visual memory, median [IQR]	0.48 [0.31]	0.59 (0.28)
Aydin 2017	MMSE (HUT), score	22 ± 5.8	23.5 ± 5.6
	MMSE (AST), score	23.9 ± 5.9	23.2 ± 5.1
	COST (HUT), score	21.4 ± 6.7	24.2 ± 5.0
	COST (AST), score	24.5 ± 4.8	23.2 ± 5.9
Bengtsson-Lindberg 2015	MMSE, score	22.5 ± 5.1	24.8 ± 4.8
Biogeau 2017	MMSE, score	21.9 ± 1	23.2 ± 1.1
Bouhanick (2014)	MMSE score ≤24 (%)	24.1	23.9
Centi 2017	MMSE, score	27.1 ± 1.4	28.4 ± 1.1
	WTAR, score	45.7 ± 2.2	46.1 ± 3.2
Coutaz 2011	MMSE, score	24.0 ± 5.5	25.6 ± 4.4
Curreri 2016	MMSE, score	27.1 ± 1.7	27.3 ± 1.8
Enrique Asensio 2011	MMSE, score	15.5 ± 7.2	16.1 ± 7.9
Frewen 2014	MMSE, score; median [IQR]	25 [22–27]	25 [23–27]
	MoCA, score; median [IQR]	29 [27–30]	29 [28–30]
	Color Trail 1 (seconds), median [IQR]	56 [43–75]	51 [39–68]
	Color Trail 2 (seconds), median [IQR]	103 [82–132]	103 [82–182]
	Letter fluency, score	11 ± 5	12 ± 5
	Word fluency, score	20 ± 7	21 ± 7
	Visual reasoning, score	2.9 ± 1.3	3 ± 1.4
	CRT (ms), median [IQR]	508 [446–586]	490 [436–556]
	SART, score	386 ± 108	369 ± 98
	Picture recall, score	2.9 ± 1.2	3.2 ± 1.1
	Picture recognition, score; median [IQR]	6 [5–6]	6 [5–6]
	Immediate recall, score	5.5 ± 1.7	5.8 ± 1.7
	Delayed recall, score	5.6 ± 2.3	6.1 ± 2.3
Huang, 2017	MMSE, score	26.4 ± 1.26	26.8 ± 1.09
Matsubayashi, 1997	MMSE, score	25.8 ± 3.8	26.5 ± 3.4
	HDSR, score	22.5 ± 4.3	24.5 ± 4.6
	VCPS, score	1569 ± 664	1934 ± 384
Mehrabian, 2010	CEP, score	50 ± 24	56 ± 22
Pilleri 2013	MMSE, score	25.1 ± 3.9	24.7 ± 3.0
	FAB, score	13.2 ± 3.1	14.5 ± 2.8
	TMT-A, seconds	77.2 ± 62.5	77.2 ± 76.3
	TMT-B, seconds	272.5 ± 172.2	267.4 ± 173.7
	TMT B-A, seconds	171.2 ± 125.2	159.5 ± 131.9
	Digit Span Forward, score	5.57 ± 1.0	5.51 ± 1.1
	Digit Span Backward, score	3.81 ± 1.2	3.44 ± 1.0
	Corsi test, score	4.28 ± 0.9	5.24 ± 1.1
	Verbal fluency (phonologic)	30.7 ± 11.4	29.4 ± 11.2
	Verbal fluency (semantic)	34.7 ± 10.2	35.6 ± 12.3
	ROCF Copy	26.8 ± 7.6	27.2 ± 7.4
	ROCF Reproduction	11.8 ± 7.3	13.2 ± 6.6
	Attentional matrix	40.1 ± 10.5	47.6 ± 7.6
	Immediate recall	36.7 ± 11.2	41.6 ± 9.9
	Delayed recall	6.82 ± 3.4	9.14 ± 2.9
Punchick 2016	MMSE, score	22.5 ± 5.2	21.6 ± 5.8
	MoCA, score	16.4 ± 5.0	16.4 ± 4.8
Schoon 2013	MMSE, score	24.9 ± 4.6	25.7 ± 3.9
	CAMCOG, score	79.2 ± 11.8	80.8 ± 12
Soennesyn 2014	MMSE, score; median [IQR] baseline	23 [22–26]	24 [22–26]
	MMSE, score; median [IQR] follow up	18 [11 − 23]	15 [9–20]
Soysal 2014	MMSE, score	21.0 ± 6.0	21.5 ± 6.1
Umehara 2016	MMSE, score	27 ± 3	26 ± 3
	FAB, score	13 ± 3	14 ± 2
Viramo 1999	Short MMSE (total score 25), score	21.6 ± 4	21.2 ± 4.1
Yap 2008	MMSE, score	26.7 ± 3.5	27.3 ± 3.2

All variables are presented as mean (SD) unless indicated otherwise. Ms.: metres per seconds. OH: Orthostatic hypotension. MMSE: Mini Mental State Examination. SRT: Simple reaction time. CRT: Choice reaction time. HUT: Head Up Tilt. AST: Active Standing Test. COST: Cognitive State Test. WTAR: Wechsler Test of Adult Reading. MoCA: Montreal Cognitive Assessment. SART: Sustained Attention to Response Task. HDSR: Hasegawa Dementia Scale Revised. VCPS: Visuospatial Cognitive Performance Score. CEP: Cognitive Efficiency Profile. FAB: Frontal Assessment Battery. TMT: Trail Making Test. ROCF: Rey-Osterrieth Complex Figure. CAMCOG: Cognitive and self-contained part of the Cambridge Examination for Mental Disorders of the Elderly. CDR-SB: Clinical Dementia Rating Sum of Boxes. sMMSE: shortened Mini Mental State Examination.

assess cognition using MMSE alone and to be retrospective (Biogeau et al., 2017; Schoon et al., 2013; Bouhanick et al., 2014; Punchick et al., 2016; Soysal et al., 2014; Asensio Lafuente et al., 2011; Agnoletti et al., 2015b).

3.2. Quality assessment

Table 3 presents the risk of bias quality assessment for included studies based on the Newcastle-Ottawa Scale (see Supplementary Appendix B). Eight studies were found to be of high quality, 21 studies of moderate quality and three studies of low quality.

3.3. Meta-analysis

Meta-analysis was performed on the 16 studies that reported mean MMSE scores for those with and without OH. Fig. 2 shows that OH was significantly associated with a lower mean MMSE score, difference −0.51 (95% CI: −0.85, −0.17, p = 0.003), with high heterogeneity (I^2 = 64.9%). Egger's regression test for OH and MMSE score did not suggest publication bias (p = 0.31). Fig. 3 shows the results of the meta-analysis of the association between OH and mean MMSE scores stratified for study population. Community dwelling older adults with OH were found to have significantly lower average MMSE mean scores in comparison to those without OH (difference (95% CI): −0.38, (−0.71, −0.06), p < 0.02), with moderate heterogeneity (I^2 = 42.9%). No significant differences were found for geriatric outpatients, hospitalised patients, patients with PD or institutionalised older adults. Fig. 4 shows the forest plot of longitudinal studies reporting odds ratios for cognitive impairment in populations with OH compared to those without OH. There was an association between OH and cognitive impairment in older adults on longitudinal data [OR (95% CI): 1.19 (1.00, 1.42), p = 0.048], with high heterogeneity (I^2 = 58.9%).

4. Discussion

OH is significantly associated with a lower MMSE mean score and higher prevalence of cognitive impairment. Cognition was assessed with a wide range of assessment scales and cognitive outcomes were reported heterogeneously. Most studies reporting a significant association between OH and worse cognition assessed cognition using

Table 3
Risk of bias quality assessment (using Newcastle-Ottawa Scale).

First author, year	Selection				Comparability	Outcome			Score	Quality
	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	OH diagnosis	Adjustment for confounders	Assessment of outcome	Adequacy of duration of follow-up	Adequacy of completeness of follow-up		
Agnoletti 2015	+	+	−	+	−	+	−	−	4	Moderate
Allcock 2006	+	−	−	−	−	+	−	−	2	Low
Aydin 2017	+	+	−	+	−	+	−	−	4	Moderate
Bengtsson-Lindberg 2015	+	+	−	+	−	+	−	−	4	Moderate
Biogeau 2017	+	+	−	+	−	+	−	−	4	Moderate
Bouhanick 2014	+	+	−	+	−	+	−	−	4	Moderate
Centi 2017	+	+	+	+	−	+	−	−	5	Moderate
Coutaz 2011	+	+	−	+	−	+	−	−	4	Moderate
Curreri 2016	+	+	−	+	+ +	+	+	−	7	High
Enrique Asensio 2011	+	+	−	+	−	+	−	−	4	Moderate
Elmstahl 2014	+	+	−	−	−	+	+	−	4	Moderate
Feeney 2016	+	+	+	−	+ +	+	+	−	7	High
Frewen 2014	+	+	−	−	−	+	−	−	3	Low
Huang 2017	+	+	−	+	−	+	+	+	6	Moderate
Idiaquez 2007	+	+	+	+	−	+	−	−	5	Moderate
Kim 2012	+	+	−	+	−	+	−	−	4	Moderate
Matsubayashi 1997	+	+	−	+	−	+	−	−	4	Moderate
Mehrabian 2010	+	+	−	+	+ +	+	−	−	6	Moderate
O'Hare 2017	+	+	−	+	+ +	+	+	+	8	High
Otsuka 2014	+	+	−	−	−	+	−	−	3	Low
Peralta 2007	+	+	+	+	+ +	+	−	−	7	High
Pilleri 2013	+	+	−	+	−	+	−	−	4	Moderate
Punchick 2016	+	+	−	+	−	+	−	−	4	Moderate
Schoon 2013	+	+	+	−	−	+	−	−	4	Moderate
Soennesyn 2014	+	+	−	+	+ +	+	+	+	8	High
Sonnesyn 2009	+	+	−	+	+ +	+	−	−	6	Moderate
Soysal 2014	+	+	−	+	−	+	−	−	4	Moderate
Struhal 2014	+	+	+	+	−	+	−	−	5	Moderate
Umehara 2016	+	+	−	+	+	+	−	−	5	Moderate
Viramo 1999	+	+	−	+	+ +	+	+	−	7	High
Wolters 2016	+	+	−	+	+ +	+	+	−	7	High
Yap 2008	+	+	−	+	+ +	+	+	+	8	High

+ quality criterion met; − quality criterion not met. Study with score between 0 and 3 is considered of low quality, 4–6 as moderate quality, 7–9 as high quality. OH: orthostatic hypotension.

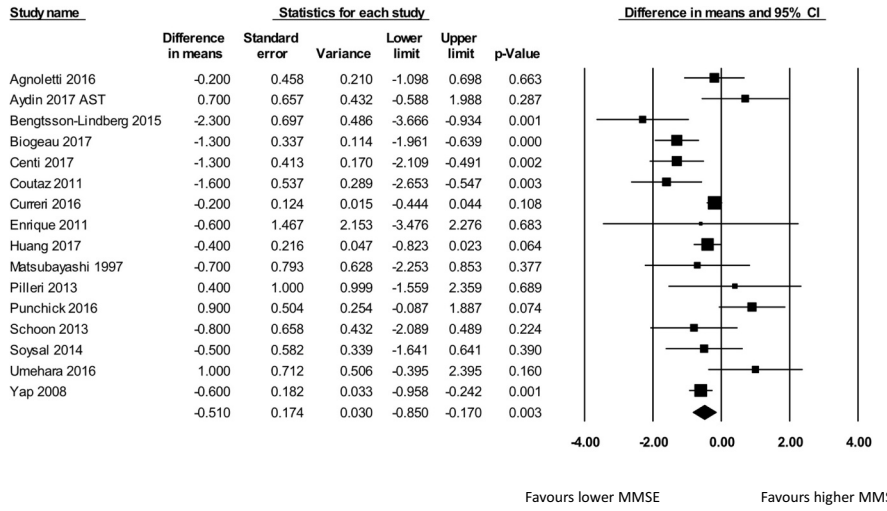

Fig. 2. Meta-analysis showing the pooled estimate on the overall association between OH and MMSE scores. CI: confidence intervals. I^2 = 64.9%.

multiple cognitive assessment scales or reported diagnosis of dementia.

MMSE was originally developed to quickly assess and grade cognition (Folstein et al., 1975), however it has limitations, including poor identification of executive dysfunction (Allone et al., 2018); floor effects in patients with limited education or advanced dementia; ceiling effect for those with mild cognitive impairment; and, the possibility of

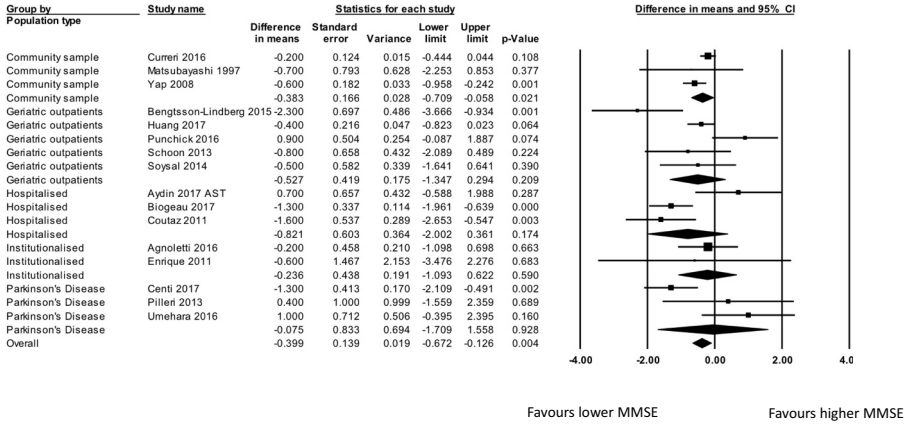

Fig. 3. Meta-analysis showing the association between OH and MMSE scores of studies stratified by study population. CI: confidence intervals.

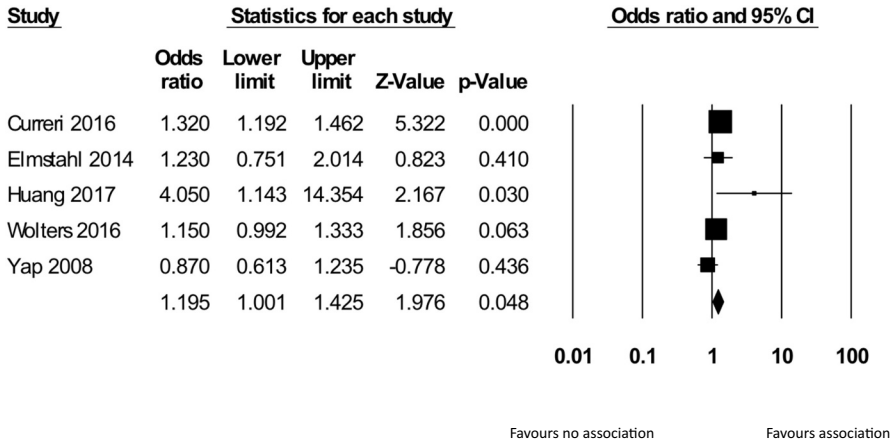

Fig. 4. Meta-analysis showing on the association between OH and incident cognitive impairment. CI: confidence intervals. $I^2 = 58.9\%$.

learning effects with repeated use (Houx et al., 2002) (Devenney and Hodges, 2017). A recent meta-analysis indicated that MMSE may be most useful for ruling out cognitive impairment in the community setting, and that in other settings it should be used in combination with other assessment tools (Mitchell, 2009). Therefore, it is possible that the use of MMSE as a measure underestimates the magnitude of the association between OH and cognition.

This systematic review confirmed high prevalence rates of OH in older adults, particularly in geriatric outpatients, PD and dementia. This is consistent with a recent study demonstrating higher rates of OH among frail older adults (Liguori et al., 2018). Bengtsson-Lindberg et al. reported that nearly two thirds of participants with OH and dementia did not have OH symptoms (Bengtsson-Lindberg et al., 2015). This highlights the importance of assessing older patients for OH, particularly those with dementia, regardless of symptomatology.

4.1. Potential mechanisms for the association between OH and worse cognition

The findings of this systematic review and meta-analysis do not prove a causal association between OH and worse cognition, however, we postulate that changes in cerebral perfusion in OH may lead to cognitive decline. During rapid changes in systemic blood pressure, cerebral perfusion is maintained by cerebral autoregulation, particularly dynamic cerebral autoregulation (Novak and Hajjar, 2010; Poda et al., 2012). Studies of cerebral blood flow (CBF) during upright tilt have identified reduced CBF in frontal regions in OH in both healthy elderly and patients with Alzheimer's type dementia (Siennicki-Lantz et al., 1999). Also, rapid changes in systolic blood pressure has been associated with worse physical performance (Mol et al., 2018b). The studies by Centi et al. and Peralta et al. reporting an association between worse cognitive performance in patients with OH and PD during upright tilt (compared to supine), support the hypothesis that cerebral blood flow change in OH can affect cognition (Centi et al., 2017; Peralta et al., 2007). Mortality rates are higher in older patients with both low and high diastolic blood pressure, and this is more marked in cognitively impaired patients (Cacciatore et al., 2005). Decrease in blood flow to the brain may lead to formation of subcortical infarcts and white matter hyperintensities (Centi et al., 2016). Amyloid deposition may also be implicated: ischaemic stress is associated with amyloid deposition in the human brain (Jendroska et al., 1995) and cerebral hypoperfusion in rodents is associated with increased expression of ß-amyloid precursor protein (Shi et al., 2000). It is possible, however, that autonomic dysfunction is a marker of neurodegenerative disease that causes both OH and cognitive change, rather than a causative factor (Allcock et al., 2006).

4.2. Strengths and limitations

To the best of our knowledge, this is the first systematic review and meta-analysis on the association between OH and cognition in all older adult populations. One limitation of our review is that studies reporting cognitive tests other than MMSE were excluded from the meta-analysis due to the small numbers and range of tests used. Furthermore, there was high heterogeneity in the meta-analysis of the association between MMSE scores and OH. We were unable to perform additional age- and sex-specific analyses due to the limited reported data. Future pooled estimates at patient-level may provide better insights into the

association between OH and cognition, as prevalence of OH and cognitive impairment increases with age (Rutan et al., 1992).

More studies diagnosed OH using the AST, rather than HUT. Aydin et al. found that OH diagnosed using HUT was more predictive of adverse clinical outcomes than OH diagnosed by AST (Aydin et al., 2017); therefore, the association between OH and worse cognition may have been underestimated in this review.

5. Conclusions

Orthostatic hypotension is associated with lower MMSE scores and increased rates of cognitive impairment. Whether the association between OH and worse cognition is causative remains uncertain, and requires further longitudinal studies using comprehensive cognitive assessment tools and repeated assessment for OH. OH is highly prevalent, especially in patients with dementia, and is often asymptomatic. We recommend that older patients, especially those with cognitive decline and dementia, are routinely assessed for OH.

Author contributions

Study conception by ABM and KWL. Search strategy developed by VTVN, RI and EMR. Screening and data extraction performed by VTVN and RI; conflicts resolved by EMR, ABM and KWL. VTVN and RI performed the data analysis with assistance from SS. Manuscript development led by RI with all authors involved in analysis and editing of manuscript.

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Declarations of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.exger.2019.02.017.

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